Tetrahedron Letters 51 (2010) 2193–2194

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formation of trialkyl quinoline-2,3,4-tricarboxylates by reaction of isatin, dialkyl acetylenedicarboxylates, and sodium *O*-alkyl carbonodithioates

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ARTICLE INFO

Article history:
Received 2 December 2009
Revised 6 February 2010
Accepted 19 February 2010
Available online 23 February 2010

Keywords:
Quinoline-tricarboxylate
Isatin
S-Nucleophile
Acetylenic ester
Carbon disulfide

ABSTRACT

An efficient one-pot synthesis of quinoline-2,3,4-tricarboxylates is described by reaction of isatin (indoline-2,3-dione) and electron-deficient acetylenic esters in the presence of sodium *O*-alkyl carbonodithioates, themselves prepared by addition of sodium hydride to a solution of an alcohol in CS_2.

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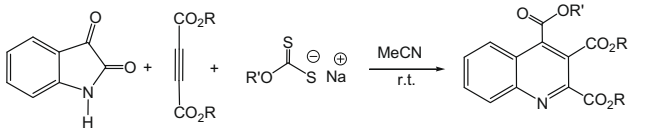
Quinolines are an important group of heterocyclic compounds, several derivatives of which have been found to possess useful biological activity such as antimalarial, antibacterial, anti-asthmatic, antihypertensive, and anti-inflammatory.[1–4] In addition, quinolines are valuable synthons for the preparation of nano- and meso-structures with enhanced electronic and photonic functions.[5–7] Due to their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed toward the development of new quinoline-based structures as well as new methods for their construction.[8–11] A number of procedures have been reported for the synthesis of quinolines involving a variety of metal catalysts and Lewis acids.[12–15] However, many of these methods suffer from harsh reaction conditions, long reaction times, low yields, difficulties in work-up, and the use of stoichiometric and/or relatively expensive reagents.

As part of our current studies on the development of new routes in heterocyclic synthesis,[16–18] we report an efficient synthetic route to quinoline-2,3,4-tricarboxylates. Thus, the reaction of isatin (indoline-2,3-dione, **1**) with dialkyl acetylenedicarboxylates **2**, in the presence of sodium *O*-alkyl carbonodithioates **3** at room temperature, produced trialkyl quinoline-2,3,4-tricarboxylates (**4**) in good yields[19] (Scheme 1). Nucleophiles **3** were derived from alcohols (R'OH) and carbon disulfide in the presence of sodium hydride (10 mol %).

The structures of compounds **4a**–**4k** were assigned based on their IR, ^{1}H NMR and ^{13}C NMR spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited three singlets for the methoxy protons at δ = 3.89, 3.95 and 3.97, together with characteristic signals for the aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to the ester carbonyl groups of **4a** were observed at δ = 165.4, 165.5 and 165.6. The mass spectrum of **4a** displayed the molecular ion peak at m/z = 303. The ^{1}H and ^{13}C NMR spectra of **4b**–**4k** were similar to those of **4a** except for the alkyl moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.



1

2	R
a	Me
b	Et

3	R'
a	Me
b	Et
c	^{n}Pr
d	^{i}Pr
e	^{t}Bu
f	Bn
g	Allyl

4	R	R'	Yield (%)
a	Me	Me	87
b	Me	Et	85
c	Me	^{n}Pr	90
d	Me	^{i}Pr	82
e	Me	^{t}Bu	86
f	Me	Bn	92
g	Me	Allyl	83
h	Et	Me	83
i	Et	Et	92
j	Et	Bn	89
k	Et	^{n}Pr	87

Scheme 1. Synthesis of compounds **4**.

Although the mechanistic details of the reaction are not known, a plausible rationalization[20] may be advanced to explain the

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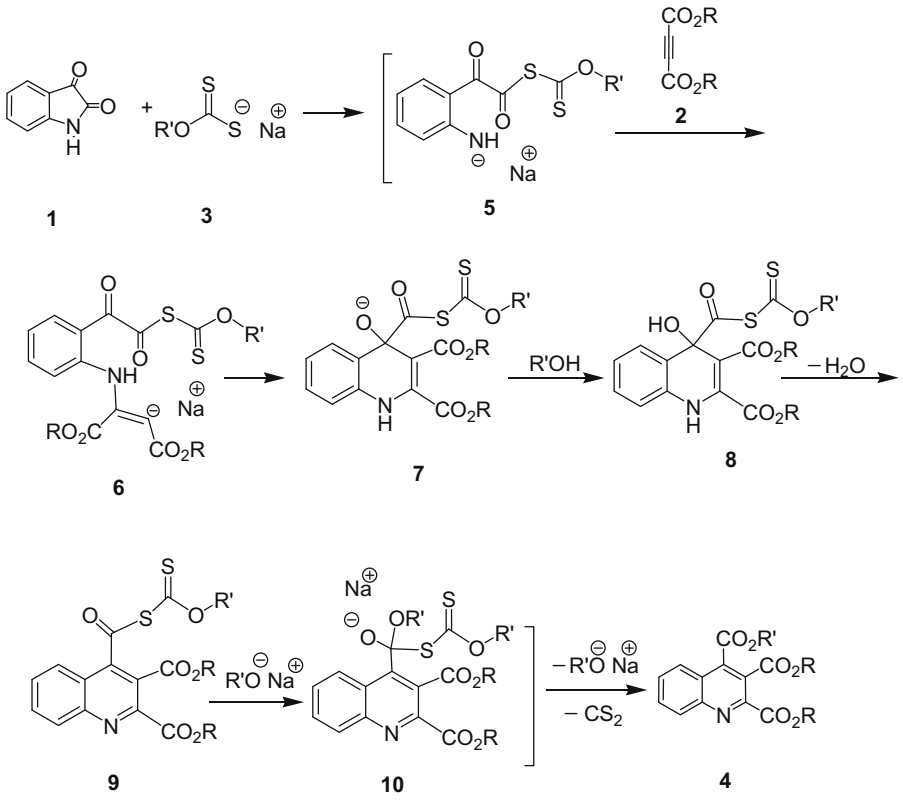
0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.02.107



Scheme 2. A proposed mechanism for the formation of compounds **4**.

product formation (Scheme 2). Presumably, the reaction starts with the formation of salt **5**, followed by addition of the dialkyl acetylenedicarboxylate **2** to generate intermediate **6**. This intermediate undergoes a cyclization reaction to afford **7**, which is protonated by the alcohol (used to form **3** in situ) to generate **8**. Intermediate **8** is converted into thioanhydride **9** by elimination of H_2O. The alkoxide ion then attacks **9** to generate **10**, which finally undergoes a fragmentation reaction to produce product **4**.

In conclusion, we have developed a convenient, one-pot method for the synthesis of trialkyl quinoline-2,3,4-tricarboxylates using isatin and acetylenic esters in the presence of sodium *O*-alkyl carbonodithioates. The present method may be considered as a practical route for the synthesis of quinoline ring systems.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.107.

References and notes

1. Bilker, O.; Lindo, V.; Panico, M.; Etiene, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R. *Nature* **1998**, *392*, 289.
2. Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021.
3. Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374.
4. Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543.
5. Aggarwal, A. K.; Jenekhe, S. A. *Macromolecules* **1991**, *24*, 6806.
6. Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **1999**, *32*, 7422.
7. Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315.
8. Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765.
9. Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819.
10. Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, *41*, 8523.
11. Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467.
12. Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485.
13. Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 7249.
14. Bose, D. S.; Kumar, R. K. *Tetrahedron Lett.* **2006**, *47*, 813.
15. Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811.
16. Yavari, I.; Mirzaei, A.; Moradi, L.; Hosseini, S. *Tetrahedron Lett.* **2008**, *49*, 2355.
17. Yavari, I.; Moradi, L.; Mokhtarporyani-Sanandaj, A.; Mirzaei, A. *Helv. Chim. Acta* **2007**, *90*, 392.
18. Yavari, I.; Karimi, E. *Tetrahedron Lett.* **2008**, *49*, 6433.
19. *Compounds* **4**: *General procedure*. To a stirred solution of the alcohol (2 mmol) in CS_2 (0.35 g, 5 mmol) containing NaH (10 mol %), was added, at rt, a solution of 0.30 g of isatin (**1**) (2 mmol) and the acetylenic ester (**2**) (2 mmol) in 2 mL of MeCN. After completion of the reaction [2–4 h; TLC (EtOAc/hexane 2:1)], the solvent was evaporated, and the residue was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/EtOAc 4:1)].
Trimethyl quinoline-2,3,4-tricarboxylate (**4a**): Orange oil, yield: 0.53 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1721, 1719, 1717, 1549, 1431, 1308, 1265, 1230, 1195. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (3H, s, MeO), 3.95 (3H, s, MeO), 3.97 (3H, s, MeO), 7.62 (1H, d, ^3J = 7.8 Hz, CH), 7.77 (1H, t, ^3J = 7.8 Hz, CH), 7.95 (1H, t, ^3J = 7.8 Hz, CH), 8.16 (1H, d, ^3J = 7.8 Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.9 (MeO), 53.0 (MeO), 53.1 (MeO), 122.8 (C), 123.5 (C), 125.4 (CH), 129.8 (CH), 130.2 (CH), 131.9 (CH), 139.8 (C), 147.3 (C), 147.7 (C), 165.4 (C=O), 165.5 (C=O), 165.6 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 303 (M^+, 10), 288 (43), 273 (85), 244 (75), 187 (80), 129 (100), 59 (45). Anal. Calcd for $C_{15}H_{13}NO_6$ (303.26): C, 59.41; H, 4.32; N, 4.62. Found: C, 59.75; H, 4.36; N, 4.65.
4-tert-Butyl, 2,3-dimethyl quinoline-2,3,4-tricarboxylate (**4e**): Yellow oil, yield: 0.59 g (86%). IR (KBr) (ν_{max}/cm^{-1}): 1732, 1725, 1720, 1545, 1425, 1380, 1362, 1210, 1159, 1100. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (9 H, s, Me_3C), 3.73 (3H, s, MeO), 3.84 (3H, s, MeO), 7.35 (1H, d, ^3J = 7.9 Hz, CH), 7.42 (1H, t, ^3J = 7.9 Hz, CH), 7.82 (1H, t, ^3J = 7.9 Hz, CH), 8.16 (1H, d, ^3J = 7.9 Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4 (Me_3C), 52.3 (MeO), 53.0 (MeO), 86.4 (Me_3C), 122.2 (C), 123.3 (C), 124.8 (CH), 129.5 (CH), 130.4 (CH), 132.0 (CH), 141.2 (C), 147.6 (C), 149.2 (C), 165.5 (C=O), 165.6 (C=O), 165.7 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 345 (M^+, 7), 330 (32), 288 (54), 286 (65), 244 (71), 229 (39), 185 (73), 129 (80), 57 (100). Anal. Calcd for $C_{18}H_{19}NO_6$ (345.35): C, 62.60; H, 5.55; N, 4.06. Found: C, 62.52; H, 5.49; N, 4.08.
20. Kravchenko, D. V.; Kysil, V. M.; Ilyn, A. P.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Ivachtchenko, A. V. *Synth. Commun.* **2006**, *36*, 911.